Perfetti 4

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Response to the Bromacil Reregistration Standard: Product and Residue Chemistry Studies (MRID #'s 43460601, 43461601 and 43375001, CBRS #'s 14595, 14765 and 14766, Barcodes: D209884, D209883 and D208561).

FROM: R. B. Perfetti, Ph.D., Chemist
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Health Effects Division (7509C)

RB Perfetti

THRU: William J. Hazel, Ph.D., Section Head
Reregistration Section 2
Chemistry Branch II: Reregistration Support
Health Effects Division (7509C)

W. J. Hazel

TO: Esther Saito, Chief
Reregistration Branch
Special Review & Reregistration Division (7508W)

Attached are three reviews of product and residue chemistry studies submitted in response to the bromacil Reregistration Standard. These reviews were completed by Dynamac Corporation under supervision of CBRS, HED. They have undergone secondary review in the branch and have been revised to reflect Agency policies.

1. The qualitative nature of bromacil residues in/on pineapple is adequately understood. The residue to be regulated is bromacil.

2. The available pineapple field trial data satisfy residue data requirements for the use of bromacil in/on pineapple. The submitted data indicate that residues of bromacil *per se* will not exceed the established tolerance of 0.1 ppm in/on pineapples harvested 125-215 days following the last of two applications of bromacil (80% WP) totalling 10 lb ai/A (1.25x the maximum seasonal rate) or 20 lb ai/A (2.5x). No additional data are required; however, the registrant should

specify a PHI in all relevant labels. The data indicate that a PHI of 125 days would be appropriate.

3. Although the pineapple fruit used to obtain processing data did not bear measurable residues, the submitted pineapple processing study is adequate. The registrant indicated that the plants treated at 2.5x exhibited signs of phytotoxicity. Residues of bromacil were nondetectable (<0.04 ppm) in/on pineapple harvested 215 days after two broadcast applications of bromacil (80% WP), first at 12 lb ai/A before planting followed by a second application prior to floral induction at 8 lb ai/A for a total seasonal rate of 20 lb ai/A (2.5x). Residues were also nondetectable in/on juice and bran processed from the pineapples. No food/feed additive tolerances are required.

4. The submitted GC/ECD method is adequate for collecting data on residues of bromacil *per se* in/on pineapples and pineapple processed commodities.

5. The submitted storage stability data indicate that residues of bromacil *per se* are stable in pineapples under frozen storage conditions (-15 C) for up to 18 months and in pineapple beverage juice and bran at -15 to -25 C for 99 and 139 days, respectively.

6. Product Chemistry GLN's 61-2 and 61-3 for EPA Reg. Nos. 352-346 and 352-413 are satisfied.

If you need additional input please advise.

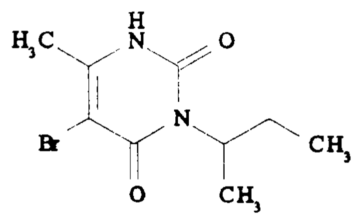
Attachment 1: Bromacil Product and Residue Chemistry Reviews

Attachment 2: Confidential Appendix to the Product Chemistry Review

cc (With Attachments 1 and 2): RBP, Bromacil Reregistration Standard File and Bromacil Subject File.

cc (Without Attachments): RF

BROMACIL



Shaughnessy No. 012301; Case 0041

(CBRS No. 14765; DP Barcode D209884)

REGISTRANT'S RESPONSE TO RESIDUE CHEMISTRY DATA REQUIREMENTS

BACKGROUND

The Bromacil Guidance Document (9/82) concluded that acceptable data on pineapple and pineapple processed commodities were available and that no additional data were required. However, the Residue Chemistry Chapter of the Second Round Review (SRR) Registration Standard dated 8/89 noted that the submitted field trial data did not reflect residues in pineapple harvested at the minimum inferred PHI of 150 days and that the submitted processing data did not satisfy requirements for processing studies because pineapples bearing measurable weathered residues were not used. Data depicting the magnitude of the residue of bromacil in/on pineapple and pineapple processed fractions were required. In addition, the SRR required data depicting residues of bromacil in/on pineapple forage. However, as pineapple forage is no longer listed as a regulated commodity in the updated (6/94) Table II of Subdivision O, data in/on pineapple forage are no longer required.

In response to outstanding data requirements, E. I. du Pont de Nemours and Company has submitted (1994; MRID 43461601) data depicting the magnitude of the residue in pineapple and its processed fractions. These data are reviewed here for their adequacy in fulfilling residue chemistry data requirements. The Conclusions and Recommendations stated in this review pertain only to residues of bromacil in/on pineapple and processed pineapple commodities.

The qualitative nature of the residue in plants is adequately understood based on an acceptable orange metabolism study and a recently reviewed pineapple metabolism study (D209883). The residue of concern and the residue to be regulated in plants is bromacil *per se*. The qualitative nature of the residue in ruminants is adequately understood. This is a category 3 [40 CFR §180.6 (a)(3)] situation with respect to meat and milk, and therefore no tolerances are needed for these commodities. A poultry metabolism study is presently not required since bromacil is not registered for use on crops that are used as poultry feed.

Tolerances of 0.1 ppm for residues of bromacil (5-bromo-3-*sec*-butyl-6-methyluracil) in/on citrus and pineapple fruit have been established and are expressed in terms of bromacil *per se* (40 CFR §180.210). No tolerances exist for residues of bromacil in animal commodities and no food/feed additive tolerances have been established.

Adequate methods are available for tolerance enforcement and data collection. A GLC method with microcoulometric detection is available for tolerance enforcement and is listed in PAM Vol. II as Method I. Additional methods deemed adequate for purposes of tolerance enforcement include a GLC method with electron-capture detection (ECD), published in PAM Vol. II as Method B, and an improved GLC method using a thermionic nitrogen/phosphorus detector (GLC/ECD) used for data collection. These methods have not undergone validation by the Agency; therefore, they may be considered only as confirmatory methods for determining residues of bromacil *per se*.

No maximum residue limits (MRLs) for bromacil have been established by Codex for any agricultural commodity. Therefore, no compatibility questions exist with respect to U.S. tolerances.

CONCLUSIONS AND RECOMMENDATIONS

1a. The available pineapple field trial data satisfy residue data requirements for the use of bromacil in/on pineapple. The submitted data indicate that residues of bromacil *per se* will not exceed the established tolerance of 0.1 ppm in/on pineapples harvested 125-215 days following the last of two applications of bromacil (80% WP) totalling 10 lb ai/A (1.25x the maximum seasonal rate) or 20 lb ai/A (2.5x). No additional data are required; however, the registrant should specify a PHI in all relevant labels. The data indicate that a PHI of 125 days would be appropriate.

1b. Although the pineapple fruit used to obtain processing data did not bear measurable residues, the submitted pineapple processing study is adequate. The registrant indicated that the plants treated at 2.5x exhibited signs of phytotoxicity. Residues of bromacil were nondetectable (<0.04 ppm) in/on pineapple harvested 215 days after two broadcast applications of bromacil (80% WP), first at 12 lb ai/A before planting followed by a second application prior to floral induction at 8 lb ai/A for a total seasonal rate of 20 lb ai/A (2.5x). Residues were also nondetectable in/on juice and bran processed from the pineapples. No food/feed additive tolerances are required.

2. The submitted GC/ECD method is adequate for collecting data on residues of bromacil *per se* in/on pineapples and pineapple processed commodities.

3. The submitted storage stability data indicate that residues of bromacil *per se* are stable in pineapples under frozen storage conditions (-15 C) for up to 18 months and in pineapple beverage juice and bran at -15 to -25 C for 99 and 139 days, respectively.

DETAILED CONSIDERATIONS

Residue Analytical Methods

In conjunction with the pineapple field and processing study, DuPont submitted a method description (1994; MRID 43461601) for the analysis of bromacil in pineapple and its processed fractions. Bromacil residues were determined using a modification of the GC/ECD method previously reviewed (R. Perfetti, CBRS Nos. 12786, 12787, and 12802, DP Barcodes D196552, D196549 and D196553, 7/27/94) and deemed adequate for data collection on pineapple. The modifications included using dichloromethane (DCM) as the extracting solvent instead of chloroform. In addition, when analyzing bran samples, the bromacil standard was combined with a control bran matrix in order to account for matrix effects.

Briefly, residues are extracted with DCM, concentrated, dissolved in NaOH, cleaned up by passing through a C18 column, partitioned into ethyl acetate, and analyzed using GC/ECD.

Method validation was performed by analyzing triplicate or quadruplicate samples of control pineapple, beverage juice, and bran fortified at 0.04-0.25 ppm with bromacil. Recoveries of bromacil from the three matrices (30 samples) were 73-120%. The limit of quantitation (LOQ) is 0.04 ppm and the limit of detection is 0.01 ppm. Concurrent recoveries were 70-111% from pineapple, beverage juice, and bran control samples fortified with bromacil at 0.04-0.25 ppm (Table 1). Chromatograms, calculations, and raw data were presented. Bromacil residues were nondetectable (<0.04 ppm) in/on all control samples. Analyses were performed by the Hawaiian Sugar Planters' Association (HSPA) analytical laboratory.

Table 1. Concurrent method recoveries of bromacil from fortified control samples.

Commodity	Fortification Level (ppm)	% Recovery (ppm)
Pineapple	0.04	70, 98
	0.1	91
	0.25	90
Juice	0.04	98
	0.1	97
Bran	0.04	85, 111
	0.1	85, 102

The submitted GC/ECD method is adequate for collecting data on residues of bromacil in/on pineapple and pineapple processed commodities.

Magnitude of the Residue in Plants and Processed Food/Feeds

Pineapple and Processed Commodities. A tolerance of 0.1 ppm has been established for bromacil *per se* in/on pineapple (40 CFR §180.210). There are no established tolerances for residues of bromacil in pineapple processed fractions.

A REFs search dated 1/15/94 indicated that bromacil formulated as a 80% WP (Reg. No. 352-287) and a 80% DF (Reg. No. 352-546) are registered for multiple applications to pineapples grown in HI and FL. The first treatment may be made at 1.6-4.8 lb ai/A as a ground broadcast application before the plant begins to grow. The remaining treatments may be made either as directed interline applications prior to floral differentiation at 1.6-3.2 lb ai/A or as broadcast treatments at 1.6 lb ai/A after the plant is 8 months old but prior to floral differentiation. The formulations are also registered for application to ratoon crops at 0.8-3.2 lb ai/A to be applied using ground equipment after harvesting the plant crop but before differentiation. The maximum seasonal application rates are 8 lb ai/A and 3.2 lb ai/A to the plant and ratoon crops, respectively. In PR, bromacil is registered for use on pineapples at 0.8-3.2 lb ai/A to be applied immediately after planting and before plants begin to grow. A PHI is not specified. Replanting of treated areas to any crop other than pineapples within 2 years after application is prohibited.

DuPont submitted (1994; MRID 43461601) data from three tests conducted in HI depicting residues of bromacil in/on pineapple and its processed commodities. Two ground applications of the 80% WP were made to the plots; the first broadcast application was made prior to planting and the second interline application was made just prior to floral induction. At one site (Maui), one plot was treated with 6 lb ai/A followed by 4 lb ai/A for a total seasonal rate of 10 lb ai/A (1.25x) and another plot was treated with 12 lb ai/A followed by 8 lb ai/A for a total seasonal rate of 20 lb ai/A (2.5x). At the second site (Oahu), one plot was treated with 6 lb ai/A preplant followed by 4 lb ai/A 29 days after floral induction for a total seasonal rate of 10 lb ai/A (1.25x). One control plot was established at each site. Two to three composite samples were harvested from each control and treated plot at a PHI of 215 (Maui) and 125 days (Oahu). The registrant stated that the PHIs were longer than the 120-day PHI stated in their protocol because the fruit did not ripen early enough to yield suitable fruit for processing. The registrant also explained that the treatment of the plants at the Oahu site 29 days after floral induction did not significantly impact the samples as no flowers had emerged at the time of the last treatment. In addition, the registrant stated that pineapple plants treated at 2x were stunted and some fruits were smaller and malformed.

Within 2 hours of harvest, control and treated pineapple fruit samples from the Maui site were transported to the Maui Pineapple Company where a control and a 2.5x treated sample were immediately processed into slices, beverage juice, ionex juice, pulp, and bran using simulated commercial processing procedures. Control, 1.25x, and 2.5x treated fruit samples were homogenized at the cannery and frozen (-15 C) along with the processed fractions. The RAC and processed samples were shipped frozen to HSPA for analysis. Immediately after harvest, samples from the Oahu site were trucked at ambient temperature to HSPA where they were homogenized and stored frozen (-15 C) until analysis. The registrant stated that overall, pineapple RAC and processed fractions were held in frozen storage (-15 C) for up to 150 days (approximately 5 months).

A freezer storage study was initiated after receipt of the samples at the analytical lab. One sample of pineapple fruit and two each of juice and bran were fortified at 0.4 ppm with bromacil and stored frozen with unfortified control samples at -15 to -25 C. At each freezer storage interval, one to two fortified samples of each matrix, a control, and a freshly fortified control sample were analyzed. Pineapple fruit, beverage juice, and bran samples were analyzed after 113, 99, and 139 days of freezer storage, respectively; recoveries were 79-93% In addition, previously reviewed storage stability data (R. Perfetti, 7/27/94) indicate that residues of bromacil *per se* are stable at -15 C for up to 18 months in/on pineapple fruit. CBRS concludes that the storage stability data adequately supports the submitted study. No additional storage stability data are required.

Seven treated pineapple fruit samples (five samples at 1.25x and two treated at 2.5x), one juice sample, three bran samples, and one to five control samples of each matrix were analyzed for bromacil residues using the GLC/ECD method described in the Residue Analytical Methods section above. Residues of bromacil were nondetectable (<0.04 ppm; LOQ) in all of the control and treated samples.

In summary, the available pineapple field trial data satisfy the residue data requirements for the use of bromacil in/on pineapple. Geographic representation is adequate. The test state of HI accounts for virtually all of the U.S. pineapple acreage. The submitted data indicate that residues of bromacil will not exceed the established tolerance of 0.1 ppm in/on pineapples harvested 125-215 days following the last of 2 applications of the bromacil (80% WP) at 10 lb ai/A (1.25x the maximum seasonal rate) and 20 lb ai/A (2.5x). No additional data are required, however, the registrant should specify a PHI on all relevant labels. The data indicate that a PHI of 125 days would be appropriate.

Although the pineapple fruit used to obtain processing data did not bear measurable residues, the submitted pineapple processing study is adequate. The registrant indicated that the plants treated at 2.5x showed evidence of phytotoxicity. Residues of bromacil were nondetectable (<0.04 ppm) in/on pineapple harvested 215 days after two broadcast applications of bromacil (80% WP), first at 12 lb ai/A before planting followed by a second application prior to floral induction at 8 lb ai/A for a total seasonal rate of 20 lb ai/A (2.5x). Residues were also nondetectable in/on juice and bran processed from the pineapples. No food/feed additive tolerances are required.

MASTER RECORD IDENTIFICATION NUMBERS

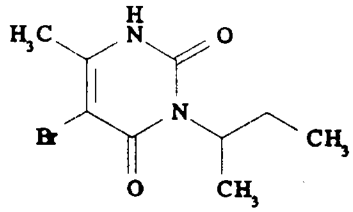
The citation for the MRID document referred to in this review is presented below:

43461601 Amoo, J.S. (1994) Magnitude of Residue of Bromacil in Pineapple Fruit and its Processed Fractions Following Application of Hyvar X Herbicide: DuPont Lab Project Number: AMR 2227-92. Unpublished study prepared by E.I. du Pont de Nemours and Company and the Hawaiian Sugar Planters' Association. 123p.

AGENCY MEMORANDA

CBRS Nos.:	12786, 12787, and 12802,
DP Barcodes:	D196552, D196549 and D196553
Subject:	Response to the Bromacil Reregistration Standard: Residue Chemistry Studies
From:	R. Perfetti, CBRS
To:	E. Saito, SRRD
Dated:	7/27/94
MRIDs:	42967301, 42967501 and 42967401

BROMACIL



Shaughnessy No. 012301; Case 0041

(CBRS No. 14766; DP Barcode D209883)

REGISTRANT'S RESPONSE TO RESIDUE CHEMISTRY DATA REQUIREMENTS

BACKGROUND

The Bromacil Guidance Document (9/82) concluded that the qualitative nature of the residue in plants was adequately understood based on data pertaining to the metabolism of [^{14}C]bromacil in grasses and citrus. However, the Residue Chemistry Chapter of the Second Round Review (SRR) Registration Standard dated 8/15/89 concluded that data depicting the uptake, distribution, and metabolism of ring-labeled [^{14}C]bromacil in pineapple and a member of the citrus crop group were required. In response, E. I. du Pont de Nemours & Company submitted data (1994: MRID 43460601) pertaining to the metabolism of [^{14}C]bromacil in greenhouse grown pineapple. These data are reviewed here for their adequacy in fulfilling residue chemistry data requirements. The Conclusions and Recommendations stated in this review pertain only to plant metabolism data requirements.

The qualitative nature of the residue in citrus is adequately understood. The residue of concern and the residue to be regulated in citrus is bromacil *per se*. The qualitative nature of the residue in ruminants is adequately understood. This is a category 3 [40 CFR §180.6 (a)(3)] situation with respect to meat and milk, and therefore no tolerances are needed for these commodities. A poultry metabolism study is presently not required since bromacil is not registered for use on crops that are used as poultry feed.

Tolerances of 0.1 ppm for residues of bromacil in/on citrus and pineapples have been established and are expressed in terms of bromacil *per se* (40 CFR §180.210).

Adequate methods are available for tolerance enforcement and data collection. A GLC method with microcoulometric detection is available for tolerance enforcement and is listed in PAM Vol. II as Method I. Additional methods deemed adequate for purposes of tolerance enforcement include a GLC method with electron-capture detection, published in PAM Vol. II as Method B, and an improved GLC method using a thermionic nitrogen/phosphorus detector. These methods have not undergone validation by the Agency; therefore, they may be considered only as confirmatory methods for determining residues of bromacil *per se*.

No maximum residue limits (MRLs) for bromacil have been established by Codex for any agricultural commodity. Therefore, no compatibility questions exist with respect to U.S. tolerances.

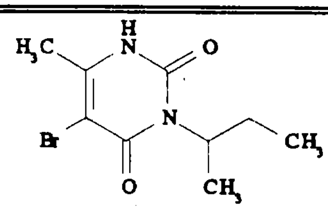
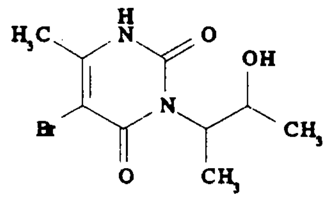
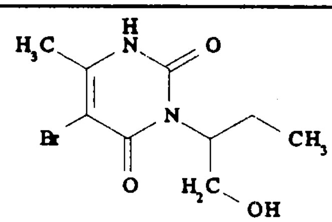
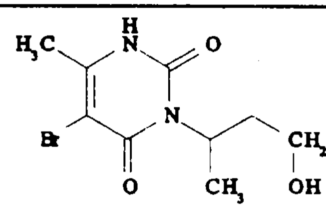
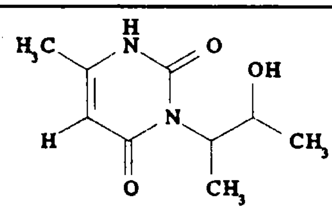
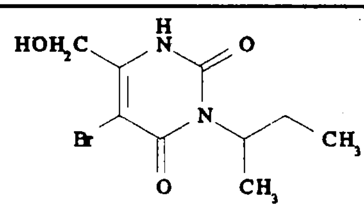
CONCLUSIONS/RECOMMENDATIONS

1. The qualitative nature of bromacil residues in/on pineapple is adequately understood. Bromacil residues are readily taken up by pineapple plants from the soil and translocated into leaves and fruits following application of [2-^{14}C]bromacil at 0.8-1x the maximum registered rate. Total ^{14}C-residues in the pineapple fruit treated with two soil applications (4.8 + 3.2 lb ai/A [1x]) or a soil and foliar application (4.8 + 1.6 lb ai/A [0.8x]) were 2.13 and 0.32 ppm, respectively. Total ^{14}C-residues reached a maximum of 12.1 ppm in leaves from the lx-treated plants collected at a 2-month posttreatment interval (PTI). Analyses of leaves and fruit from a third group of plants treated with a single foliar application at 1.6 lb ai/A (0.2x) indicated that bromacil does not readily penetrate the pineapple leaf.

2. Greater than 90% of the total ^{14}C-residues in/on pineapple fruit were identified/characterized. The major metabolites identified in fruit from plants treated with two soil applications (1x) were free and conjugated forms of Metabolite D (32.8% TRR; 0.69 ppm), Metabolite C (21.5% TRR; 0.45 ppm), and Metabolite B (12.1% TRR; 0.25 ppm). Debrominated Metabolite D (JY674) accounted for 5.6% of the TRR (0.12 ppm), and the remainder of the radioactivity was accounted for by 4 unknowns, each $\leq$9.3% of the TRR. Metabolite D (72.2% TRR; 0.23 ppm) was identified in fruit from plants treated at 0.8x (soil/foliar); Metabolites B, C, and JY674 were not detected. Bromacil *per se* was not detected in pineapple fruit from plants treated at 1x but was detected (0.02 ppm) in fruit from plants treated at 0.8x. The registrant stated and CBRS agrees that the trace amount of bromacil detected in the fruit was probably due to contact of the fruit with the [^{14}C]bromacil treated leaves and does not reflect translocation of bromacil into the fruit. The data indicate that metabolism of bromacil in pineapple fruit proceeds from hydroxylation of the *sec*-butyl side chain followed by conjugation of the hydroxylated metabolites as previously reported for rats and goats. The metabolism differs from that in oranges where metabolism of bromacil proceeds from hydroxylation of the methyl side chain.

The molecular structures of bromacil and its metabolites identified in/on pineapple fruits and leaves are presented in Figure 1.

Figure 1. Bromacil and its metabolites in pineapple (MRID 43460601).

Common Name Chemical Name	Structure	Substrate
Bromacil 5-bromo-3-*sec*-butyl-6-methyluracil		Pineapple leaves
Metabolite D 5-bromo-3-(2-hydroxy-1-methylpropyl)-6-methyluracil		Pineapple fruit and leaves
Metabolite C 5-bromo-3-(*a*-hydroxymethylpropyl)-6-methyluracil		Pineapple fruit and leaves
Metabolite B 5-bromo-3-(3-hydroxy-1-methylpropyl)-6-methyluracil		Pineapple fruit and leaves
JY674 (debromo Metabolite D) 3-(2-hydroxy-1-methylpropyl)-6-methyluracil		Pineapple fruit and leaves
Metabolite A 5-bromo-3-*sec*-butyl-6-hydroxymethyluracil		Pineapple leaves

[a] Additional metabolite standards used in this metabolism study but not detected in any of the fruit or leaf samples were Metabolite F (3-*sec*-butyl-6-methyluracil and Metabolite G (5-bromo-6-methyluracil).

DETAILED CONSIDERATIONS

Directions for use

The bromacil 80% WP (Reg. No. 352-287) and the 80% DF (Reg. No. 352-546) formulations are registered for multiple applications to pineapples grown in HI and FL. The first treatment may be made at 1.6-4.8 lb ai/A as a ground broadcast application before the plants begin to grow. The remaining treatments may be made either as directed interline applications prior to floral differentiation at 1.6-3.2 lb ai/A or as broadcast treatments at 1.6 lb ai/A after the plant is 8 months old but prior to floral differentiation. Bromacil is also registered for application to ratoon crops at 0.8-3.2 lb ai/A using ground equipment, after harvesting the planting crop but before differentiation. The maximum seasonal application rates are 8 lb ai/A and 3.2 lb ai/A to the planting and ratoon crops, respectively. In PR, bromacil is registered for use on pineapples at 0.8-3.2 lb ai/A to be applied immediately after planting and before plant begins to grow. A PHI is not specified. Replanting of treated areas to any crop other than pineapples within two years after application is prohibited.

Qualitative Nature of the Residue in Plants

Du Pont submitted data (1994: MRID 43460601) pertaining to the metabolism of bromacil in pineapples. [^{14}C]Bromacil labeled at the C-2 position of the ring and formulated as a 80% WP had a specific activity of 3.65-3.87 μCi/mg and a radiochemical purity of >97%. Three groups of pineapple plants grown in the greenhouse of the Du Pont Experimental Station in Wilmington, DE were treated with [^{14}C]bromacil. For Group-1, eight pots containing a sandy loam soil were treated with two soil applications; the first application was made just prior to planting at 4.8 lb ai/A followed by a second directed interline spray application at 3.2 lb ai/A when the plants were differentiating (flowering). The applied rate was 1x the maximum permitted on the label. For Group-2, one pot containing a sandy loam soil received a soil application just prior to planting at 4.8 lb ai/A followed by a directed spray to the foliage at 1.6 lb ai/A when the plant was in the redbud stage (0.8x). For Group-3, nine 2-year old plants in the redbud stage growing in clay pots containing a sandy loam soil/metromix (1:1) were treated once with a foliar spray at 1.6 lb ai/A (0.2x).

A whole plant was sampled at each harvest interval by cutting the plant just above the soil surface. Samples from Group-1 and Group-3 were harvested periodically up to 22- and 6-month PTIs, respectively (Table 1). The Group-2 plant was harvested at a 22-month PTI. The registrant explained that final harvests occurred when the fruit began to turn yellow and smell ripe.

Upon harvest, the fruit were separated from the leaves and crown and frozen (temperature not specified) for up to 18 weeks prior to extraction and analysis at the Du Pont Experimental Station in DE. Previously submitted storage stability data indicate that residues of bromacil *per se* are stable in pineapple fruit at -15 C for up to 18 months (R. Perfetti, CBRS Nos. 12786, 12787, and 12802, DP barcodes D196552, D196549, and D196553, 7/27/94). No additional storage stability data are required in support of this metabolism study.

Total Radioactive Residue (TRR)

Triplicate aliquots of homogenized plant tissues were combusted and radioassayed by liquid scintillation spectroscopy (LSS). Leaf samples from Group-3 plants were rinsed with acetonitrile (ACN)/H_2O (1:1, v/v) to remove surface residues. These residues and other liquid fractions were radioassayed directly by LSS. The limits of detection for fruit and leaves were 0.03 ppm and 0.011 ppm, respectively. Sample calculations and raw data were submitted. The TRRs, expressed as bromacil equivalents, are presented in Table 1. All analyses were performed at Du Pont, Wilmington, DE.

Table 1. Total radioactive residues (TRR) in fruits and leaves from pineapple treated with [^{14}C]bromacil at 6.4-8 lb ai/A (0.8-1x).

Group Matrix	Posttreatment Interval	[^{14}C]Bromacil Equivalents (ppm)[a]
Group-1 (1x)[b]		
Leaves	Day-0[c]	0.011
	2-Week	2.91
	1-Month	5.96
	2-Month	12.1
	4-Month	7.37
	15-Month[d]	2.95
	15.5-Month	3.92
	16-Month	3.68
	17-Month	5.00
	19-Month	7.28
	22-Month	7.71
Fruit	22-Month	2.13
Group-2 (0.8x)		
Leaves	22-Month	4.01
Fruit	22-Month	0.26
Group-3 (0.2x)		
Leaves	2-Month	2.78
	4-Month	2.37
	6-Month	1.21
Fruit	2-Month	<0.01
	4-Month	0.019
	6-Month	0.022

[a] Average of triplicate analyses. Data were obtained from Table 4 in MRID 43460601.
[b] Group-1 plants were treated with two soil applications; Group-2 plants were treated with one soil and one foliar application, and Group-3 plants were treated with one foliar application.
[c] Day-0 sample was an unplanted crown; 0.011 ppm=detection limit.
[d] Leaves were sampled at the 15-month PTI just prior to second application of bromacil.

A subsample of the Group-2 fruit at a 22-month PTI (TRR = 0.26 ppm) was also fractionated into peeled fruit and peel to determine residue distribution in these fractions; the TRR were determined by combustion/LSS. The distribution of radioactive residues were 45% of the TRR (0.14 ppm) in the pulp and 55% TRR of the TRR (0.12 ppm) in the peel.

Extraction and Hydrolysis of Residues

Frozen homogenized leaf and fruit samples were separately extracted with acetonitrile (ACN):H_2O (9:1, v/v). The extracted residues were washed with hexane, concentrated, and filtered prior to HPLC analysis. The hexane wash was discarded and the unextractable residues were not analyzed further. In some instances, similar leaf HPLC fractions from multiple HPLC injections were combined, concentrated, and diluted with water. The combined leaf HPLC fractions and whole extracts from pineapple leaves and fruit were subjected to enzyme (β-glucosidase, pH 5, 0.01 N sodium acetate buffer, incubated at 37 C for 48 hours) or acid hydrolysis (1N HCl, 80 C for 12 hours) and further HPLC analyses.

To demonstrate that bromacil is stable under the extraction and analysis conditions, the registrant also extracted freshly fortified pineapple fruit samples and analyzed them using the PAM enforcement method and a modification of the method. Virtually 100% of the radioactivity was extracted as undegraded bromacil.

Characterization of Residues

HPLC analyses were performed on a system equipped with a UV absorbance detector at 277 or 280 nm and a radioisotope detector with reversed-phase columns and two H_2O/ACN solvent systems. Radioactive compounds were identified by comparing their retention times to those of the unlabeled reference standards.

Identity of bromacil in 2-month leaf samples was confirmed by TLC co-chromatography with the bromacil standard. Identity of Metabolite D in leaf samples was confirmed by LC/MS; its identity in fruit samples was confirmed by coelution with the partially purified [^{14}C]Metabolite D isolated from leaves. Identities of Metabolites B and C in fruit and leaf samples were confirmed by comparing retention times with standards using two HPLC solvent systems. Representative TLC, HPLC, and LC/MS chromatograms were submitted. The distribution and characterization/identification of ^{14}C-activity in pineapple fruit and foliage is summarized in Tables 2 and 3. It is noted that the TRRs from the fractionation procedures are slightly different than the TRRs obtained by combustion/LSS. The registrant explained that the samples may not have been homogenous when sampled for combustion/LSS.

Table 2. Distribution of TRR in fruit and foliage samples from pineapple plants treated with [^{14}C]bromacil at 6.4-8 lb ai/A (0.8-1x).

Fraction	% TRR[a]	ppm	Characterization/Identification
Group-1 Fruit, 22-month PTI (2.12 ppm)			
ACN/H_2O	98.2	2.08	HPLC analysis identified Metabolite B (6.3% TRR; 0.14 ppm), Metabolite D (11.5% TRR; 0.25 ppm), Metabolite C (4.5% TRR; 0.14 ppm) and debrominated metabolite B (JY674; 6.4% TRR; 0.14 ppm). At least 7 unknowns accounted for ~70% of the TRR. To further characterize the residues, the extract was subjected to enzyme or acid hydrolysis.
Enzyme hydrolyzate	98.2	2.08	HPLC analysis identified Metabolite B (13.4% TRR; 0.28 ppm), Metabolite D (12.4% TRR; 0.26 ppm), Metabolite C (8.0% TRR; 0.17 ppm), Metabolite A (3.2%; 0.066 ppm) and JY674 (5.9% TRR; 0.12 ppm). Unknowns accounted for ~55% of the TRR.
Acid hydrolyzate (1N HCl)	98.2	2.08	HPLC analysis identified Metabolite B (12.1% TRR; 0.25 ppm), Metabolite D (32.8% TRR; 0.68 ppm), Metabolite C (21.5% TRR; 0.45 ppm), and JY674 (5.6% TRR; 0.12 ppm). Approximately 28% of the TRR was accounted for by 4 unknowns, each ≤9.3% of the TRR. Identity of Metabolite D was confirmed by coelution with the partially purified Metabolite D identified from leaves. Identity of Metabolite C was confirmed by comparing retention times with standards using two HPLC solvent systems.
Solids	1.8	0.04	N/A=not analyzed further.
Group-2 Fruit, 22-month PTI (0.32 ppm)			
ACN/H_2O	99.9	0.32	HPLC analysis identified bromacil (6% TRR; 0.02 ppm) and Metabolite D (72.2% TRR; 0.23 ppm). Approximately 27% of the TRR was accounted for by 4 unknowns, each ≤11.5% of the TRR. Identity of Metabolite D was confirmed by coelution with the partially purified Metabolite D identified from leaves.
Solids	0.1	0.0	N/A
Group-1 Leaves, 2-month PTI (12.2 ppm)			
ACN/H_2O	98.0	12.0	HPLC analysis identified bromacil (6.9% TRR; 0.84 ppm), Metabolite C (5.2% TRR; 0.63 ppm) and Metabolite D (43.5% TRR; 5.3 ppm). The presence of bromacil was confirmed by TLC. At least 6 unknowns accounted for approximately 36% of the TRR.
Solids	2.0	0.24	N/A

(continued; footnotes follow)

Table 2 *(continued)*.

Fraction	% TRR[a]	ppm	Characterization/Identification
Group-1 Leaves, 15-month PTI (2.79 ppm)			
ACN/H_2O	91.6	2.56	HPLC analysis identified Metabolite D (21.6% TRR; 0.6 ppm). Three areas of radioactivity accounted for ~48% of the TRR that was not characterized.
Solids	8.4	0.23	N/A
Group-1 Leaves, 19-month PTI (7.98 ppm)[b]			
ACN/H_2O	99.9	7.97	HPLC analysis identified Metabolite D (28.0% TRR; 2.2 ppm) and Metabolite C (7.2% TRR; 0.56 ppm). Five areas of radioactivity accounted for ~65% of the TRR. To further characterize the residues, similar HPLC fractions were combined and subjected to enzyme or acid hydrolysis.
Enzyme hydrolyzate	100	7.98	HPLC analysis identified Metabolite D (32.7% TRR; 2.6 ppm), Metabolite C (13.4% TRR; 1.0 ppm), Metabolite B (6.1 TRR; 0.48 ppm) and JY674 (11.3% TRR; 0.88 ppm). Approximately 37% of the TRR was accounted for by 5 areas of radioactivity each area accounting for ≤11.4% of the TRR.
Acid hydrolyzate (1N HCl)	100	7.98	HPLC analysis identified Metabolite D (28.8% TRR; 2.2 ppm), Metabolite C (25.6% TRR; 2.0 ppm), Metabolite B (8.8 TRR; 0.69 ppm) and JY674 (14.8% TRR; 1.2 ppm). Approximately 22% of the TRR was accounted for by 4 areas of radioactivity each area accounting for ≤6.5% of the TRR.
Solids	0.1	0.0	N/A
Group-1 Leaves, 22-month PTI (8.26 ppm)			
ACN/H_2O	93.0[b]	7.69	HPLC analysis identified Metabolite D (9.5% TRR; 0.78 ppm) and Metabolite C (8.4% TRR; 0.69 ppm). Five areas of radioactivity accounted for ~74% of the TRR. To further characterize the residues, the leaf extract was subjected to mild acid hydrolysis.
Acid hydrolyzate	93.0[c]	7.69	HPLC analysis identified Metabolite D (17.1% TRR; 1.41 ppm), Metabolite C (16.6% TRR; 1.37 ppm), and Metabolite B (6.3% TRR; 0.52 ppm). JY674 was tentatively identified (14.8% TRR; 1.22 ppm). The remaining 6 areas of radioactivity each accounted for ≤9.3% of the TRR. Identity of Metabolite D was confirmed by LC/MS. Identity of Metabolites B and C were confirmed by comparing retention times with standards using two HPLC solvent systems.
Solids	7.0	0.58	N/A

[a] Data were normalized by the registrant.
[b] Data obtained from Table 9 in MRID 43460601.
[c] Data regarding components identified/characterized in this fraction were obtained from Figure 7 (b); TRR values were calculated by reviewer.

Table 3. Summary of characterization and identification of radioactive residues in/on fruits and leaves harvested at a 22-month PTI from pineapple treated with [^{14}C]bromacil at 6.4-8 lb ai/A (0.8-1x).

Component/Fraction	Group-1 Fruit (1x)		Group-2 Fruit (0.8x)		Group-1 Leaves (1x)	
	% TRR	ppm	% TRR	ppm	% TRR	ppm
Bromacil	ND[a]	ND	6.0	0.02	ND	ND
Metabolite D	32.8	0.68	72.2	0.23	17.1	1.41
Metabolite C	21.5	0.45	ND	ND	16.6	1.37
Metabolite B	12.1	0.25	ND	ND	6.3	0.52
JY674	5.6	0.12	ND	ND	14.8	1.22
Total identified	72.0	1.5	78.2	0.25	54.8	4.52
Unknowns	28.1[b]	0.6	27.5[c]	0.09	38.2	3.15
Total identified/ characterized	100.1	2.10	105.7	0.34	93.0	7.69
Unextractable	1.8	0.04	0.1	0.00	7.0	0.58

[a] ND=nondetectable (<0.03 ppm for fruit and <0.011 ppm for leaves).
[b] TRR was accounted for by 4 unknowns, each ≤9.3% of the TRR.
[c] TRR was accounted for by 4 unknowns, each ≤11.5% of the TRR.

Analysis of Group 3 (0.2x) leaf and fruit samples indicated that bromacil does not easily penetrate the pineapple leaf. At a 4-month PTI, 46% of the applied bromacil was still on the leaf surface. In addition, residue levels in the fruit (<0.01-0.022 ppm) and crown (<0.010-0.032 ppm) were much lower than in the leaves (1.21-2.78 ppm). HPLC analysis of the fruit indicated that Metabolite D was the major component of the radioactive residue.

In summary, the qualitative nature of bromacil residues in/on pineapple is adequately understood. Total radioactive residues (expressed as bromacil equivalents) are readily taken up by pineapple plants from the soil and translocated into leaves and fruits following application of [2-^{14}C]bromacil at 0.8-1x the maximum registered rate. Total ^{14}C-residues in the pineapple fruit treated with two soil applications (4.8 + 3.2 lb ai/A [1x]) or a soil and foliar application (4.8 + 1.6 lb ai/A [0.8x]) were 2.13 and 0.32 ppm, respectively. Total ^{14}C-residues reached a maximum of 12.1 ppm in leaves from the lx-treated plants at a 2-month PTI. Analyses of leaves and fruit from a third group of plants treated with a single foliar application at 1.6 lb ai/A (0.2x) indicated that bromacil does not readily penetrate the pineapple leaf.

Greater than 90% of the total ^{14}C-residues in/on pineapple fruit were identified/characterized. The major metabolites identified in fruit from plants treated with two soil applications (1x) were free and conjugated forms of Metabolite D (32.8% TRR), Metabolite C (21.5% TRR) and Metabolite B (12.1% TRR). Debrominated Metabolite D (JY674) accounted for 5.6% of the TRR and the remainder of the radioactivity was comprised of four unknowns, each accounting for ≤9.3% of the TRR. Metabolite D (72.2% TRR) was identified in fruit from plants treated at 0.8x (soil/foliar); Metabolites B, C, and JY674 were not detected. Bromacil *per se* was not detected in pineapple fruit from plants treated at 1x but was detected at 6% of the TRR (0.02 ppm) in fruit from plants treated at 0.8x. The registrant stated and CBRS agrees that the trace amount of bromacil detected in the fruit was probably due to contact of the fruit with the [^{14}C]bromacil treated leaves. A minor amount of Metabolite A (3.2%) was detected after enzyme hydrolysis of the 2-month PTI leaf sample from plants treated at 1x.

Metabolite D comprises a significant portion of the residue in pineapples. It was observed at a level 12 times that of the bromacil concentration in pineapple fruit. Therefore, while the residue to be included in the tolerance expression for pineaples will be bromacil, CBRS will use a 12X factor for the risk assessment. In the crop field trials no bromacil was observed at a limit of quantitation of 0.04 ppm; therefore the exposure which will be used will be 0.5 ppm. DRES has indicated that the present tolerances use up only ca. 1% of the new RfD for bromacil. Therefore significantly less than 100% RfD will be taken up even when this additional residue is incorporated into the risk assessment.

The data indicate that metabolism of bromacil in pineapple fruit proceeds from hydroxylation of the *sec*-butyl side chain followed by conjugation of the hydroxylated metabolites as previously reported for rats and goats. The metabolism differs from that in oranges where metabolism of bromacil proceeds from hydroxylation of the methyl side chain.

In conjunction with the pineapple metabolism study, the registrant extracted freshly fortified pineapple fruit and analyzed the samples using the PAM enforcement method. The method was able to detect approximately 100% of the radioactivity as undegraded bromacil.

MASTER RECORD IDENTIFICATION NUMBERS

The citation for the MRID document referred to in this review is presented below:

43460601 Schneiders, G.E. and Irelan, M.J. (1994) Uptake and Metabolism of [2-^{14}C]Bromacil in Pineapple. Laboratory Project ID: AMR 2395-92. Unpublished study prepared by E. I. du Pont de Nemours & Company. 105 p.

EPA MEMORANDA CITED IN THIS REVIEW

CBRS Nos.:	12786, 12787, and 12802,
DP Barcodes:	D196552, D196549 and D196553
Subject:	Response to the Bromacil Reregistration Standard: Residue Chemistry Studies
From:	R. Perfetti, CBRS
To:	E. Saito, SRRD
Dated:	7/27/94
MRIDs:	42967301, 42967501 and 42967401

DYNAMAC
CORPORATION
Environmental Services

Final Report

BROMACIL
Shaughnessy No. 012302
Case No. 0041
(CBRS No. 14595, DP Barcode D208561)

Registrant's Response to Product Chemistry Data Requirements

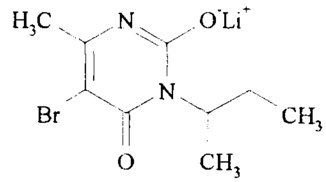
February 27, 1995

Contract No. 68-D4-0010

Submitted to:
U.S. Environmental Protection Agency
Arlington, VA 22202

Submitted by:
Dynamac Corporation
The Dynamac Building
2275 Research Boulevard
Rockville, MD 20850-3268

BROMACIL
(LITHIUM SALT)



Shaughnessy No. 012302; Case 0041

(CBRS No. 14595; DP Barcode D208561)

REGISTRANT'S RESPONSE TO PRODUCT CHEMISTRY DATA REQUIREMENTS

BACKGROUND

In response to the Bromacil SRR dated 8/15/89 and an Agency memorandum (CBRS Nos. 13133 and 13134, D198401 and D198403, 3/24/94, F. Toghrol), E. I. du Pont de Nemours and Company has submitted a single volume of product chemistry data (CBRS No. 14595; 1994; MRID 43375001) for the alternate formulation of the 21.9% lithium salt end-use product (Li EP; EPA Reg. No. 352-346). The registrant has submitted the EP data in support of the 21.9% lithium salt formulation intermediate (Li FI; EPA Reg. No. 352-413). Because the 21.9% Li EP and 21.9% Li FI are identical, the submitted 61 series data may be applied to both products.

The submission includes a Confidential Statement of Formula (CSF) dated 1/15/93 for the alternate formulation of the 21.9% Li EP, which has been reviewed by the Registration Division. The registrant was required to list the lithium salt of bromacil as the active ingredient on the CSF, and to adjust the nominal concentration and certified limits for the active ingredient accordingly. In addition, the registrant was required to update the CSF for the basic formulation of the 21.9% Li EP. A separate CSF is required for the 21.9% Li FI. The submitted data and our conclusions concerning the 21.9% Li FI are discussed below.

61-2. Description of Starting Materials and Manufacturing Process

Du Pont has submitted (1994; MRID 43375001) information concerning the suppliers and specifications of the starting materials and a description of the manufacturing process for the alternate formulation of the 21.9% lithium salt. This information is presented in the Confidential Appendix and satisfies the requirements of 40 CFR § 158.160 and § 158.162 (Guideline Reference No. 61-2) regarding starting materials and the manufacturing process for the du Pont 21.9% Li FI (EPA Reg. No. 352-413). No additional information is required.

61-3. Discussion of Formation of Impurities

Du Pont has submitted (1994; MRID 43375001) the following discussion of formation of impurities for the 21.9% lithium salt. The registrant states that the impurities of the lithium salt formulation reflect the composition of technical grade bromacil and the intentionally-added inert ingredients. Based on the conditions used in manufacturing the lithium salt and the chemical properties of the ingredients, no chemical reactions are expected between the active ingredient and the inert ingredients or between the active ingredient and the production equipment. In addition, no post-production reactions are expected between the active ingredient and any component of the product or its packaging. The 21.9% lithium product is a water-soluble liquid which is packaged in 1- and 2.5-gallon polyethylene containers. This discussion satisfies the requirements of 40 CFR §158.167 (Guideline Reference No. 61-3) regarding discussion of formation of impurities for the du Pont 21.9% Li FI (EPA Reg. No. 352-413). No additional information is required.

AGENCY MEMORANDA CITED IN THIS DOCUMENT

CBRS No(s):	14582
DP Barcode(s):	D208643
Subject:	Response to the Lithium Bromacil Reregistration Standard: Product Chemistry
From:	R. Perfetti
To:	E. Saito
Dated:	11/15/94
MRID(s):	None

MASTER RECORD IDENTIFICATION NUMBERS

A citation for the MRID document referred to in this review is presented below.

43375001 Kern, R. (1994) Product Identity, Description of Formulation Process, Formation of Impurities, and Certification of Limits for the End-Use Product Du Pont HYVAR® X-L: Laboratory Project Number: AMR 2967-94. Unpublished study prepared by Du Pont Agricultural Products. 51 p.

Case No. 0041
Chemical No. 012302

Case Name: Bromacil
Registrant: E.I. du Pont de Nemours and Company, Inc.
Product(s): 21.9% Li FI (EPA Reg. No. 352-413)

PRODUCT CHEMISTRY DATA SUMMARY

Guideline Number	Requirement	Requirement Fulfilled? [a]	MRID Number
61-1	Product Identity and Disclosure of Ingredients	N	
61-2	Starting Materials and Manufacturing Process	Y	43375001
61-3	Discussion of Formation of Impurities	Y	43375001
62-1	Preliminary Analysis	N [b]	
62-2	Certification of Ingredient Limits	N	
62-3	Analytical Methods to Verify the Certified Limits	N	
63-2	Color	N [c]	
63-3	Physical State	N [c]	
63-4	Odor	N [c]	
63-5	Melting Point	Y [d]	
63-6	Boiling Point	N/A [e]	
63-7	Density, Bulk Density or Specific Gravity	N [c]	
63-8	Solubility	N [b]	
63-9	Vapor Pressure	N [b]	
63-10	Dissociation Constant	N [b]	
63-11	Octanol/Water Partition Coefficient	N [b]	
63-12	pH	N [c]	
63-13	Stability	N [b]	
63-14	Oxidizing or Reducing Action	N	
63-15	Flammability	N	
63-16	Explodability	Y	
63-17	Storage Stability	N	
63-18	Viscosity	N	
63-19	Miscibility	N [f]	
63-20	Corrosion Characteristics	N	

[a] Y = Yes; N = No; N/A = Not Applicable. Data were submitted in response to the Bromacil SRR dated 8/15/89 and an Agency memorandum (CBRS Nos. 13133 and 13134, D198401 and D198403, 3/24/94, F. Toghrol). Data requirements followed by MRID citations reflect conclusions determined in this document (CBRS No. 14595; D208561).

[b] Data are required for the "practical equivalent" of the bromacil lithium salt TGAI.

[c] This data requirement is satisfied for the TGAI (CBRS No. 14582, D208643, 11/15/94, R. Perfetti); however, data remain outstanding concerning the MP.

[d] CBRS No. 14582, D208643, 11/15/94, R. Perfetti

[e] Not applicable because the TGAI is a solid.

[f] CBRS has concluded that waiver of this data requirement would be appropriate.

BROMACIL (DU PONT)

(CBRS No. 14595; DP Barcode D208561)

PRODUCT CHEMISTRY

(Final Report)

CONFIDENTIAL APPENDIX

1 Page(s)

Confidential Appendix to the Scientific Review of a Registration Standard Followup Report for the pesticide bromacil by the Chemistry Branch II Reregistration Support [Confidential FIFRA Trade Secret/CBI].

CONFIDENTIAL APPENDIX (CBRS NO. 14595; D208561)

61-2. STARTING MATERIALS AND MANUFACTURING PROCESS

Manufacturing process information may be entitled to confidential treatment

[redacted]

[These data satisfy the requirements of 40 CFR § 158.160 and § 158.162 (Guideline Reference No. 61-2) regarding starting materials and the manufacturing process for the du Pont 21.9% Li FI (EPA Reg. No. 352-413).]

13544

R116150

Chemical:	**Bromacil**
PC Code:	**012301**
HED File Code	**11000 Chemistry Reviews**
Memo Date:	**03/30/1995**
File ID:	**DPD209884; DPD209883; DPD208561**
Accession Number:	**412-06-0007**

HED Records Reference Center
10/24/2005